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EXAMINER
SAOUD, CHRISTINE J

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 11/05/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/722,495	SPRINGER et al.
Examiner	**Art Unit**
Christine Saoud	1647

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) [X] Responsive to communication(s) filed on *Aug 21, 2002*.

2a) [X] This action is **FINAL**. 2b) [ ] This action is non-final.

3) [ ] Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) [X] Claim(s) *1-8, 17-38, 40, and 48-67* is/are pending in the application.

4a) Of the above, claim(s) *50-67* is/are withdrawn from consideration.

5) [ ] Claim(s) _____ is/are allowed.

6) [X] Claim(s) *1-8, 17-38, 40, 48, and 49* is/are rejected.

7) [ ] Claim(s) _____ is/are objected to.

8) [ ] Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) [ ] The specification is objected to by the Examiner.

10) [ ] The drawing(s) filed on _____ is/are a) [ ] accepted or b) [ ] objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) [ ] The proposed drawing correction filed on _____ is: a) [ ] approved b) [ ] disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) [ ] The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) [ ] Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) [ ] All b) [ ] Some* c) [ ] None of:

1. [ ] Certified copies of the priority documents have been received.
2. [ ] Certified copies of the priority documents have been received in Application No. _____.
3. [ ] Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) [ ] Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) [ ] The translation of the foreign language provisional application has been received.

15) [X] Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) [X] Notice of References Cited (PTO-892)
2) [ ] Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) [ ] Information Disclosure Statement(s) (PTO-1449) Paper No(s).
4) [ ] Interview Summary (PTO-413) Paper No(s).
5) [ ] Notice of Informal Patent Application (PTO-152)
6) [ ] Other:

DETAILED ACTION

Response to Amendment

1. Claims 48-67 have been added as requested in the amendment of paper #8, filed 21 August 2002. Claims 1-8, 17-38, 40 and 48-67 are pending in the instant application.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. Any objection or rejection of record which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

4. Applicant's arguments filed 21 August 2002 have been fully considered but they are not deemed to be persuasive.

Election/Restriction

5. Newly submitted claims 50-67 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: the claims are directed to gene therapy, classified in class 514, subclass 44, which is a method of using the claimed invention. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that

product (MPEP § 806.05(h)). In the instant case the polynucleotides could be used in an entirely different manner, such as in the recombinant production of the polypeptide rather than in the newly added gene therapy methods. Burden of search is established by the separate classification of the two inventions and the necessity for non-coextensive literature searches.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 50-67 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

6. Claims 1-8, 17-38, 40 and 48-49 are under examination in the instant application.

Claim Objections

7. Claims 48-49 are objected to because of the following informalities: serine is listed twice in the first Markush group of the claims. It would appear that this double listing is an error. Appropriate correction is required.

Claim Rejections - 35 USC § 112

8. Claims 1-8, 17-38, 40 and 48-49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the substitution of position 89 with either alanine or tyrosine and the substitution of either of positions 101 or 137 with alanine, does not reasonably provide enablement for substitution of those positions with any neutral amino acid or

hydrophobic amino acid. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims for the reasons of record in paper #5.

At page 13 of the response, first paragraph, Applicant asserts that "there is ample evidence in the literature that usually small, minor local changes in a protein do not change the activity or the overall structure of the protein" and that "single amino acid substitutions usually do not alter enzyme activity". These arguments are not persuasive for a number of reasons. First, Applicant's mutated proteins (see examples in Table 1 at page 34 of the specification) have small, minor local changes which create superagonists, which clearly altered the activity and/or overall structure of the native protein. Secondly, Watson et al. is limited to single amino acid substitutions, whereas the claimed invention encompasses double and triple mutations, for which Watson et al. cannot be relied upon to provide supportive evidence of enablement. Additionally, Watson et al. was directed to single point mutations in which enzymatic activity was retained, regardless of whether it was the same. The instant claims are directed to mutants in which the modification results in a protein with increased biological activity, which would be considered an unexpected result. Therefore, the question is whether the substitution of alanine is predictive and commensurate in scope with the 13-15 other amino acid substitutions encompassed by the claims, including the substitution of multiple amino acid positions with a multitude of amino acids.

Applicant asserts that Bowie et al. teach that proteins are "surprisingly tolerant of amino acid substitutions". However, a review of Bowie et al., specifically Figure 1, demonstrates that the degree to which an amino acid is substitutable is not predictable. In other words, some amino

acid positions are surprisingly tolerant of a number of different amino acid substitutions, where other positions are highly intolerant (See Figure 1A). However, the tolerance of a particular position to substitution cannot be predicted from a single, or even a double amino acid substitution, as is the case in the instant application. In the instant application, position 89 was substituted with either tyrosine or alanine and positions 101 and 137 were only substituted with alanine. The ability of these positions to tolerate other amino acids AND retain the required activity of the claims, which is improved mitogenic agonist activity over wild-type basic fibroblast growth factor, is unpredictable at best. One could even argue that the claimed activity is an unexpected result, and therefore, clearly one could not expect that other substitutions would provide for the same result, absent evidence to the contrary.

Applicant argues at page 14 of the response that "Cunningham et al. can be used as evidence that when the mutagenesis does not change the protein structure, the function of the protein is conserved". This argument is not persuasive because the act of amino acid substitution does change protein structure. Protein structure exists on many levels, and amino acid sequence specifies the conformation of proteins and function arises from conformation, which is the three-dimensional arrangement of atoms in a structure. Some amino acid substitutions will have greater effects on conformation than others depending on the three-dimensional position of the amino acid in the protein. So the statement that mutagenesis does not change protein structure is false since structure is defined by amino acid sequence, binding within the protein molecule between amino acids, and the overall final folding the of the molecule to arrive at the final conformation.

Applicant argues at page 14 of the response that substitution of the named positions with alanine, or tyrosine for position 89, preserves protein function. This argument is not persuasive because function was altered, as indicated in the claims. The molecules which were generated are considered super agonist molecules, which is unexpected over the mere expectation of preservation of protein function. Additionally, the issue is that biological effect obtained with substitution with alanine is not predictive of the other amino acid substitutions encompassed by the claims. In support of this point, Wells et al. (U.S. Pat. No. 6,451,561) demonstrates the biological effects of the substitution of position 174 in human growth hormone with 12 different amino acids (Table XXIV). As can be seen from the comparison to wild type, some of the mutants bind with a greater affinity to the receptor and some of the mutants bind with a reduced affinity and some of the mutants are not expressed at all. Therefore, this demonstrates that substitution with alanine is not predicative of substitution with other amino acids, absent evidence to the contrary.

Additionally is should be noted that alanine is the amino acid used in mutational studies to determine the likelihood that an amino acid is important to biological function (called alanine scanning mutagenesis in the art). Alanine is used because it is the simplest mutation to interpret because it removes atoms without introducing new ones that can create additional unfavorable or favorable interactions (see Cunningham et al., U.S. Pat. 6,057,292 at column 36 line 65 to column 37, line 1). This is based on the fact that alanine has no side chains or functional groups. This is not the case with the other amino acids (except for possibly glycine, which has a hydrogen ion rather than the methyl group found in alanine). Therefore, based on structure alone, substitution

with any other amino acid would not be predictive of function, and clearly would not be predictive of an unexpected result, such as with the super agonist molecules of the instant application.

Applicant asserts that "[a]lanine and tyrosine are predictive of other neutral and/or hydrophobic amino acids because one of ordinary skill in the art can reasonably extrapolate from the substitutions with alanine and tyrosine to substitutions with other neutral and/or hydrophobic amino acids" (see response at page 14, final paragraph). However, this is an unsupported allegation and is contradicted by the experimental evidence of Wells et al. cited above, in which substitution with alanine was not predictive of substitution with tyrosine (see Table XXIV). Only position 89 was substituted with both alanine and tyrosine and positions 101 and 137 were only substituted with alanine. Based on the unpredictability in the art and the fact that alanine is not predictive of tyrosine substitution, one would not have a reasonable expectation that substitution of positions 101 and/or 137 with tyrosine, or any other hydrophobic amino acid, would result in the claimed improved mitogenic agonist activity. As stated previously, this improved activity is an unexpected result and therefore, one would not reasonably conclude that an unexpected result would be obtained with substitution with another amino acid based on the unpredictability of the art. The results which are provided in the instant specification are very limited (6) while the number of embodiments encompassed by the claims is enormous (upwards of 14 million) and are therefore, not commensurate in scope with what is being claimed.

Applicant argues at page 15 of the response that the Declaration provides evidence that the positions encompassed by the claims are on the surface of the protein and that "neutral and/or hydrophobic substitutions on the surface of the protein are accommodated and do not destroy the

structure of the protein" and therefore "the function of the protein is not changed". These assertions are not supported by any factual evidence and are not a clear representation of the teachings of the prior art. The prior art of Bowie et al. which is cited in the Declaration does not state that all neutral/hydrophobic substitutions on the surface of proteins are accommodated, but states that "most of the highly exposed positions tolerate a wide range of chemically different side chains". Furthermore, the prior art does not state that the function of the protein will not be changed. Contrary, Applicant's own specification demonstrates that biological activity is changed in that the substituted variants which were made and tested had an increased mitogenic activity, which is "unexpected" in the view of the teachings of the prior art according to the Applicant. Clearly the structure of the protein was changed, otherwise, the biological activity of the mutants would have been approximately the same as the wild-type protein. However, this is not the case, and such, one would reasonably conclude that the structure of the protein is changed.

Applicant asserts that the Declaration "provides evidence that the art was predictable at the time of the application was filed". This assertion is not agreed with for the reasons of record and for those reasons presented above and supported by the Wells reference cited above.

Applicant argues at page 16 of the response that the quantity of experimentation would be routine to generate muteins having improved mitogenic agonist activity. This argument is not persuasive. First, the instant claims encompass around the order of 14 million embodiments. This is an enormous amount of experimentation to undergo in terms of testing and selecting for those molecules which have increased mitogenic activity, as required by the claims. As to whether it is undue or not, all of the Wands factors should be considered, and this is but one.

Applicant continues on pages 16-17 of the response to address the amount of direction of guidance presented. Applicant argues that "plenty of guidance on protein mutagenesis was available" and that mitogenic agonist activity can be determined, therefore, one of ordinary skill "would have been able without undue experimentation to follow the guidance of the specification and determine whether a mutein has improved mitogenic agonist activity". This argument is not persuasive because Applicant is really stating that since there is an activity, one could just make the mutations and test to see if they meet the limitations of the claims. This is like saying as long as there is an assay for activity, it does not require undue experimentation to make any mutant with any desired activity since the activity could be tested. This is essentially a "make and test" standard for enablement, which does not appear to be the position of the Courts. Again, whether the experimentation is undue requires consideration of at least 8 factors as outlined in *In re Wands*. In terms of guidance, the instant specification has described 3 positions in basic fibroblast growth factor, when mutated to alanine, or tyrosine for position 89, results in a molecule which has increased mitogenic activity. This is the guidance in the specification. The specification asserts and applicant claims substitution of any of these amino acids, in any combination, with any one of 14 different amino acids. The guidance in the specification is not sufficient for one of ordinary skill in the art to reasonably predict that any one of the claimed 14 amino acids would reliably and predictably result in the claimed biological activity. This is because the specification does not provide reasonable guidance, in the way of examples or scientific reasoning, to support the assertion that the end result of the substitution with any of the other amino acids will result in the claimed biological activity. Because there is not a reasonable expectation that any one of the

other amino acids would work, and that any of the encompassed combinations would work (again, there are approximately 14 million possible embodiments), the guidance in the specification is quite limited, contrary to Applicant's assertions. Applicant's argument that screening for bioactivity could be done is basically a "wish to know" and the standard for an enabling disclosure is not one of making and testing. The fact pattern is directly analogous to that of Amgen Inc. v. Chugai Pharmaceuticals Co. Ltd., 18 U.S.P.Q. 2d, 1016 in that what is claimed are compounds (and methods of using such) that have yet to be isolated or characterized for the activity recited in the claims and thereby constitutes a "wish to know" rather than a reduction to practice, absent evidence to the contrary. The decisions of *In re Fisher*, Amgen Inc. v. Chugai, and *In re Wands* have been relied upon by the court in a recent CAFC decision, Genentech, Inc. V. Novo Nordisk, 42 USPQ2d, 100 (CAFC 1997) because they show that the judicial interpretation of the first paragraph of 35 U.S.C. § 112 requires that the breadth of the claims must be based upon the predictability of the claimed subject matter and no on some standard of trial and error. To argue that one can make material embodiments of the invention and then test for those that work in the manner disclosed or that the instant claims only encompass the working embodiments is judicially unsound. Unless one has a reasonable expectation that any one material embodiment of the claimed invention would be more likely than not to function in the manner disclosed or the instant specification provides sufficient guidance to permit one to identify those embodiments which are more likely to work than not without actually making and testing them, then the instant application does not support the breadth of the claims.

Applicant's comments spanning pages 17-18 regarding the presence of a repeatable process are noted. However, the point that was being made is that each substitution is a different process, unlike the process of making antibodies (which is what *Wands* was based upon). The process is not repeatable in that each mutant must be made and then tested in order to determine if it will have the required activity of the claims. In Wands, if the skilled artisan followed the guidance in that specification, one would be reasonably assured of generating a hybridoma which met the limitations of the claims. In the instant case, if one were to follow the guidance in the specification, meaning substitution of any combination of the 3 identified positions with any of the identified 14 amino acids, one would not be reasonably assured of obtaining a mutant with the required biological activity, absent evidence to the contrary. Therefore, there is not a repeatable process in the specification as filed.

Applicant argues at page 18 that working examples are not required. This point is noted. Applicant also states that "representative examples together with a statement applicable to the genus as a whole will be sufficient if one skilled in the art would expect the claimed genus could be used in that manner without undue experimentation". However, this is the point of contention and part of the basis for the rejection. The examples presented do not appear to be representative of the genus as a whole for the reasons provided above (specific reference to Cunningham and the unpredictable nature of amino acid substitution), especially in light of the number of examples presented and the number of embodiments encompassed by the claims.

Applicant asserts that the Examiner has not determined the nature of the invention. This is merely argumentative since the nature of the invention is the claimed subject matter, which was identified in the Office action and which Applicant repeated at page 19 of the response.

Applicant asserts at page 19 of the response that the Examiner did not address the state of the art. However, in making a determination of undue experimentation using the Wands factors, consideration of each factor is required, but this does not necessarily mean comment on each factor is necessarily required. Since the instant application is one that is in the biotechnology arts, it is generally recognized that the skill in that art is high. Applicant reference to the amount of work in the area of mutagenesis is noted, which is also why the skill in the art is high. However, this is just one of the factors to be considered when determining scope of enablement of the claimed invention.

Applicant addresses the predictability of the art at pages 19-21 of the response. Applicant's arguments at page 20, first paragraph, have been addressed previously. Applicant further argues that the specification teaches that substitutions at one or more of positions 89, 101, and 137 with "another neutral amino acid and/or a hydrophobic amino acid do not disrupt the structure of human bFGF" and that "conservation of the function of the mutein, i.e., the mitogenic agonist activity, is the proof of the protected protein structure". First, the teachings of the specification are not broadly substitution with "another neutral amino acid and/or a hydrophobic amino acid" because only substitution of alanine was made at all three positions, and tyrosine was only substituted at position 89. As pointed out previously, the resulting activity is unexpected, in light of the general teachings of the art, because the activity was increased and is called

superagonist activity in the specification. Further, art is supplied which demonstrates that alanine is not predictive of the other amino acids encompassed by the claims (see Wells et al.). Therefore, it is concluded that it would not be predictive to make other substitutions as encompassed by the claims and reasonably expect to obtain the unexpected result of increased mitogenic activity as was seen by the substitution of alanine at the recited positions, absent evidence to the contrary. The claims are not directed to conservation of function, but rather to an increased mitogenic activity. This is unexpected and unpredictable in light of the substitutions which are encompassed by the claims, and further including the vast number of combinations of substitutions which are encompassed. For example, cysteine is an amino acid included in the possible substitutions, but it is well known that cysteine forms disulfide bonds with other cysteine molecules. This is a very unpredictable event, further in combination with the addition of potentially 3 additional cysteines to the molecule.

At page 21 of the response, Applicant asserts that the claims are not unduly broad because they are limited "to conservative changes at only three surface positions". However, breadth is judged on a number of different levels, including, but not limited to the number of embodiments in light of the number of working examples and in light of the predictability of the art. In the instant case, there are 6 examples in the specification, fairly limited to alanine substitution, with a single tyrosine substitution. The claims encompass 14 different amino acid substitutions and encompass upwards of 14 million embodiments when combinations are accounted for. The amino acids which are encompassed by the claims have not been shown to be "conservative" substitutions, because conservation is not just one of amino acid structure, but also function. Since the claimed

function is increased activity and this is an unexpected result in light of the general teachings of the art at the time the invention was made, there is not a level of predictability present necessary to conclude that the breadth of the claims is commensurate in scope with the enabling disclosure. Therefore, in view of the Wands factors which include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and, (8) the breadth of the claims, it would require undue experimentation to practice the invention as claimed. Experimentation is undue because each embodiment would need to be made and tested because there is not a reasonable expectation that any one embodiment would possess the required activity of the claims. The guidance in the specification is not sufficient to direct the skilled artisan to those embodiments which would more likely than not possess the required activity, the number of embodiments encompassed is extremely large, predictability is lacking, there is a lack of guidance in the prior art, and the amount of experimentation is great as every mutant would need to be made and tested for activity. Therefore, experimentation would be undue and the claims are therefore, not enabled by the instant specification, absent evidence to the contrary.

Applicant insists that the truth of the Declaration must be accepted in the absence of good reasons to the contrary. Such reasons have been presented above, and therefore, the rejection is maintained.

9. Claims 1-8, 17-38, 40, 48 and 49 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 23 recite "comprising the substitution of a neutral and/or hydrophobic amino acid for one or more of the following". This recitation is confusing because it seems to imply that two amino acids could replace one of the recited amino acids. It would appear that the specification only contemplates single amino acid substitution (i.e. a one for one substitution), but the claim encompasses replacement of one amino acid with potentially two amino acids (both neutral and hydrophobic). Applicant asserts that page 8, lines 13-18 of the specification make it clear that claims 1 and 23 encompass replacement of one amino acid with one amino acid. However, although claims are read in light of the specification, limitations of the specification are not read into the claims. Therefore, the claims still seem to encompass more than one amino acid at the recited position, and are therefore, still indefinite.

Double Patenting

10. Applicant's Terminal Disclaimer filed on 26 August 2002 is proper and has been entered into the instant application.

Conclusion

11. No claim is allowed.

12. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Christine J. Saoud, Ph.D., whose telephone number is (703) 305-7519. The Examiner can normally be reached on Monday to Thursday from 8AM to 2PM. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. §§ 1.6(d) and 1.8). NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers.

Official papers filed by fax should be directed to (703) 872-9306. If this number is out of service, please call the Group receptionist for an alternate number. Official papers filed After Final rejection filed by fax should be directed to (703) 872-9307.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

CHRISTINE J. SAOUD
PRIMARY EXAMINER
Christine J. Saoud